glucamine, N-methylglucamine, lysine, arginine, ornithine, lysine methylamide, glycine ethylamide or serine methylamide.

27. A composition according to claim 10, wherein the amount of said compound is ~~50 μmol~~/l-2 mol/l.

28. A composition according to claim 10, wherein the amount of said compound is ~~100 μmol/l-1 mol/l~~ 100 mmol/l - 1 mol/l.

R E M A R K S

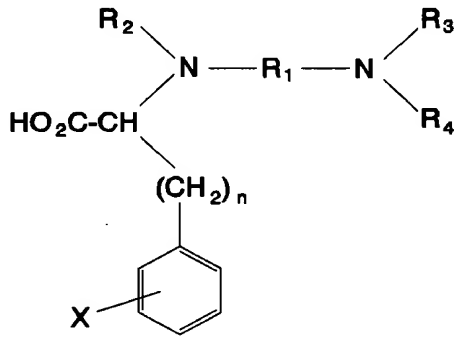
Election

Applicants hereby affirm election of Group I, claims 1-10, drawn to compounds.

Rejection Under 35 U.S.C. §103:
Johnson et al. in view of Troutner et al.

Johnson et al. (U.S. 5,057,302) discloses a genus of poly-aminocarboxylate bifunctional chelating agents having a substrate reactive moiety attached to a carboxymethyl arm. The chelating agents are bifunctional in that they can form a complex with a metal ion and also attach to a substrate via the substrate reactive moiety.

The genus of chelating agents are defined by the formula



wherein n is 0-10, R_1 can be, inter alia, $-(CH_2)_qN(R_5)(CH_2)_r-$, with q and r each being 2 or 3, R_2, R_3 and R_4 being H, CH_2CO_2H, or ortho-$CH_2C_6H_4OH$. See column 5, lines 1-41.

The X group on the phenyl ring is in the meta- or para-position and is either nitro or a substrate reactive moiety.

54

The substrate reactive moieties are described at column 6, lines 1-40. All of the exemplified X groups are nitrogen-containing structures. Compare applicants' groups Z^1 and Z^2.

Troutner et al. (U.S. 5,101,041) disclose a genus of triamine bifunctional chelating agents of the formula $R^1R^2N-(CHR)_m-N(L)-(CHR)_n-NR^2R^1$. In these compounds, the carbon atoms of the triamine backbone are substituted by the group R which is H, C_{1-3}-alkyl or benzyl. The terminal N atoms are each substituted by R^1 and R^2 which are defined at column 2, lines 40-64. It is noted that of the groups R^1 and R^2, only R^2 can be $-CH_2CO_2H$, i.e., a carboxymethyl arm.

The chelating agents of Troutner et al. are bifunctional in that they can form complexes with metal ions and can form conjugates with biomolecules. In the conjugates, a biomolecule is covalently attached to the bifunctional chelating agents via a chemical reactive group. This chemical reactive group is part of the linker/spacer group L attached to the central N atom. See the description of group L at column 2, line 67-column 3, line 22. See in particular the description of group R^3 of the linker/spacer structure.

Thus, the linker/spacer group L of Troutner et al. is attached to the central nitrogen atom of the triamine base structure. Conversely, in the compounds of Johnson et al., the substrate reactive moiety is attached to a carboxymethyl arm of a base polyamino-polycarboxylic chelator structure.

In the rejection, it is alleged that it would be obvious to incorporate the substrate reactive moiety of Johnson et al. to the position of the R group taught by Troutner et al. However, the R group does not contain the chemical reactive group for covalently bonding a biomolecule. This structure is instead found in the linker/spacer group which is attached to the central N atom.

Neither Johnson et al. nor Troutner et al. disclose a structure containing a substrate reactive moiety or chemically

reactive group for covalently bonding to biomolecules attached to a carbon atom of a triamine base structure. If one were to modify the Johnson et al. bifunctional chelating agents by moving the structure containing the substrate reactive moiety to the position taught by Troutner et al. for the structure containing the reactive group for bonding to biomolecules, the structure would be attached to a nitrogen atom within the backbone as opposed to a carbon atom. The R group of Troutner et al. provides no suggestion with respect to positioning of a structure containing a substrate reactive moiety.

Furthermore, even if, for the sake of argument, one were to modify the Johnson et al. compounds in the nonobvious manner suggested in the rejection, the resultant structure would not suggest a compound of applicants' claimed genus. As noted above, the nitrogen-containing structure $-(CH_2)_n-C_6H_4-X$ attached to the carboxymethyl arm of the Johnson et al. bifunctional chelating agents does not suggest applicants' groups Z^1 or Z^2. Moreover, group R of the compounds of Troutner et al. does not exhibit a structure in accordance with applicants' group Z^1 or Z^2.

In view of the above remarks, it is respectfully submitted that Johnson et al. and Troutner et al., taken alone or in combination, fail to establish a prima facie case of obviousness with respect to applicants' claims 1-5 and 9-10. Withdrawal of the rejection under 35 U.S.C. §103 is respectfully requested.

Rejection Under 35 U.S.C. §103
in view of Johnson et al. and Warshawsky et al.

The disclosure of Johnson et al. is discussed above.

Warshawsky et al. (U.S. 4,652,519) disclose a genus of bifunctional chelating agents having an ethylene diamine tetraacetic acid (EDTA) base structure. The EDTA compounds are substituted in the 2-position by the group $-(CH_2)_n-X$ wherein n and X are as defined at column 2, lines 36-46.

In the rejection, it is argued that Johnson et al. and Warshawsky et al. both pertain to bifunctional chelating agents

which are EDTA derivatives. The Johnson et al. genus exhibits an EDTA base structure when group R_1 is $-(CH_2)_q-$ and q is 2. However, applicants' claimed compounds do not exhibit a tri-amine base structure, i.e., diethylene triamine pentaacetic acid (DTPA), as opposed to an EDTA base structure. Thus, any suggested modification of EDTA compounds of the Johnson et al. genus gleaned form the Warshawsky et al. disclosure regarding position of the substrate reactive moiety would not yield a DTPA type compound of applicants' genus.

Furthermore, neither the group $-(CH_2)_n-C_6H_4-X$ of Johnson et al. nor $-(CH_2)_n-X$ of Warshawsky et al. exhibit a structure in accordance with applicants' group Z^1 or Z^2. Thus, even if, for the sake of argument, one were to make a nonobvious modification of a compound of the Johnson et al. genus exhibiting a DTPA base structure so as to reposition the $-(CH_2)_n-C_6H_4-X$ group, the resultant structure would still not suggest a compound of applicants' claimed genus.

As with the combination of Johnson et al. and Troutner et al., neither Johnson et al. nor Warshawsky et al., taken alone or in combination, establish a prima facie case of obviousness with respect to applicants' claimed genus. Withdrawal of the rejection under 35 U.S.C. §103 is respectfully requested.

Rejection of Claims 6-8 under 35 U.S.C. §103

The disclosures of Johnson et al., Troutner et al. and Warshawsky et al. are discussed above.

Weber et al. (U.S. 5,137,711) is relied on in the rejection of claims 6-8 for its disclosure of the use of gadolinium ions in NMR imaging. However, the disclosure of Weber et al. does not overcome the discrepancies with respect to the prior art discussed above.

Weber et al. disclose a genus of compounds having an EDTA or DTPA backbone. Thus, group A is either $-CH_2CH_2-$ or $-CH_2CH_2N(CH_2COR^1)CH_2CH_2-$. Such a structure does not anticipate or suggest a backbone in accordance with applicants' claimed compound exhibiting groups Z^1 and Z^2.

In view of the above remarks, withdrawal of the rejection under 35 U.S.C. §103 is respectfully requested.

Respectfully submitted,

Brion P. Heaney (Reg. No. 32,542)
Attorney for Applicants

MILLEN, WHITE, ZELANO & BRANIGAN, P.C.
Arlington Courthouse Plaza I
2200 Clarendon Boulevard, Suite 1400
Arlington, Virginia 22201
(703) 243-6333

Filed: March 22, 1993

BPH:kdp
kdp50:sch1199.amd